American Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

A GROUP OF NEWER THERAPEUTIC AIDS

See article on Modern Medicinals, p. 192.

Since 1825 *June 1946*

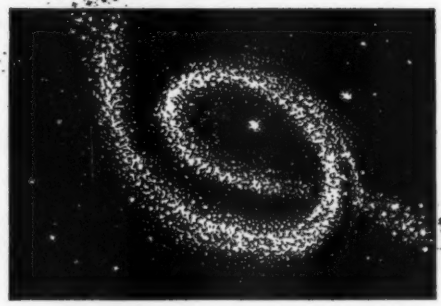
American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription, $3.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 30 Cents — Back Numbers, 50 Cents

Entered as Second-Class Matter March 27, 1937, at the Post Office at Philadelphia, Pa.
Under Act of March 3, 1879

A solar system is born



This is an astronomer's picture of one of the truly stupendous creations of nature. It is a spiral nebula—a vast mass of incandescent matter into which the solar system could be placed many times over. According to astronomers, in the millions of years to come the massive fragments will cool and solidify, forming planets to revolve around the central sun. Here, in the birth of a solar system, are expressed various fundamental physical laws which give the universe purpose and direction.

From the movements of the stars and the planets to the tiny atom, fundamental laws govern everything in the universe. In the field of retail pharmacy, laws of human behavior and economics govern the degree of success which a business may enjoy. The Lilly Policy, which embraces quality of product, progressive research, and ethical marketing practices, attempts equitably to apply these laws for the benefit of all who come beneath its scope. The Lilly Policy is your Commercial Bill of Rights, your guarantee of straightforward, fair dealing.

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Report

TO AMERICAN PHARMACISTS

The Parke-Davis campaign to better acquaint the public with the profession of pharmacy is continuing in the SATURDAY EVENING POST. This "Know Your Pharmacist Better" series of full-page messages was launched in September, 1944, and each advertisement since that time has carried its story to a potential audience of over fourteen million readers.

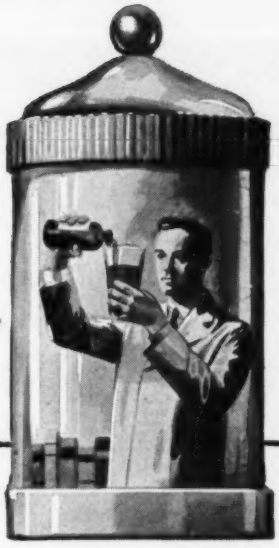
Each message is designed to accomplish a definite public relations mission . . . to bring added prestige to the calling by painting out a specific health service rendered by pharmacists.

Specimens of a number of the advertisements are reproduced on this page, and the response to them and to the others in the series has been most enthusiastic. Thousands of reprints have appeared in windows and on counters. Hundreds of pharmacists have written letters showing their appreciation of the campaign—the first constructive, continuing public relations effort devoted to furthering the interests of the profession.

PARKE, DAVIS & COMPANY

DETROIT 32 • MICHIGAN

in the materia medica of modern endocrine therapy



Protection of the fetus endangered by spontaneous abortion is a prime indication for PROLUTON intramuscularly or PRANONE orally. In pregnant women with a tendency to abortion, adequate dosages during calculated menstrual periods, or in the presence of emotional or physical stress, or in the event of cramps and spotting, have greatly increased the number of pregnancies carried safely to term.

Corpus luteum hormone therapy also is prescribed for dysmenorrhea due to a hypermotile (oversensitive) uterus and for functional uterine bleeding.

PROLUTON, corpus luteum hormone (progesterone in oil), for intramuscular injection; ampules of 1 cc. containing 1, 2, 5 and 10 mg.; boxes of 3, 6 and 50 ampules.

PRANONE, orally effective progestin (anhydrohydroxy-progesterone); tablets of 5 and 10 mg.; boxes of 20, 40, 100 and 250 tablets.

Trade-Marks PROLUTON and PRANONE—Reg. U. S. Pat. Off.

Schering CORPORATION · BLOOMFIELD, NEW JERSEY
In Canada, Schering Corporation Limited, Montreal

SCHERING

In the severe depressions of the menopause marked by apathy and psychomotor retardation

Many women in the climacteric period develop a true reactive depression, characterized by apathy, psychomotor retardation and despondency.

• This depressive syndrome is frequently progressive; and, unless promptly and effectively treated, may seriously impair the patient's normal capacity for useful living.

• In such cases, Benzedrine Sulfate helps to reawaken mental alertness and optimism, and to restore the savor and zest of life—especially when administered in conjunction with such fundamental measures as electric shock and estrogenic therapy.

• Obviously, Benzedrine Sulfate should not be used for the casual case of low spirits or normal physiologic depression, as distinguished from true prolonged mental depression. Smith, Kline & French Laboratories, Philadelphia, Pa.

BENZEDRINE SULFATE

Tablets *Elixir*

(RACEMIC AMPHETAMINE SULFATE, S. K. F.)

AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

Vol. 118. JUNE, 1946 No. 6

CONTENTS

E D I T O R I A L

NEW HORIZONS

THIS issue of the *Journal* contains a review presenting a number of the newer therapeutic aids that have been released over the past few years. Although this list was not intended to be comprehensive, it does show the diversity of products that now are available to the medical practitioner in the treatment and prevention of disease. It also conveys to the thoughtful reader a number of important facts that have been mentioned editorially before but which will, by their great significance, stand repetition.

One is impressed by the rapidly changing functions of the professional pharmacist as compared with only a few years back. Today, he is far less a compounder and far more a consultant on the availability and selection of therapeutic agents. As such he can be, and is, on a far higher plane in his relationship with the medical profession for he serves them on an equal level and so gains much more respect and prestige than when his practice was simply carrying out their written orders to the best of his ability. Some pharmacists today decry the diminishing number of polypharmacal combinations that require compounding skill, but we frankly wonder whether many of these combinations, so confidently prescribed in past years, accomplished all that might be expected from their list of ingredients. Many unrecognized chemical and physiological incompatibilities must surely have taken place in view of our present knowledge of the likelihood of such an occurrence. Those who have engaged in pharmaceutical research know how often a seemingly harmless combination proves to be unstable, inert, or otherwise objectionable when studied carefully and not simply judged by appearance alone, which was the old criterion.

Changes in pharmaceutical practice have caused many changes in the pharmaceutical curriculum and still others are yet to come. It does not suffice to learn simply by rote the name and dose of the many new drugs. To be the real ally of the physician a pharmacist must be as well-grounded as the physician in all the basic sciences and be able to discuss therapy with him without any sense of in-

feriority. This requires more emphasis on certain of the biological sciences than has been given in many of our colleges to date. Far too much emphasis is given botany and pharmacognosy than can be justified in view of modern needs and too little is given to zoology, physiology, pharmacology, and biochemistry.

Even the general public today is well-informed by press and radio on health matters and many new drugs. The pharmacist who is less well-informed than his customers on new therapy can hardly command their respect and have them look to him for advice and as serving the health needs of the community which he so often claims by advertisement. The days of mystery and ignorance about medicine and pharmacy are over and no longer can ignorance be adroitly cloaked by secrecy.

The "new horizon" in pharmacy is indeed salutary for it is increasing the prestige of pharmacists with the other health professions, with government and with the public in general; and this is not wishful thinking. All along the line one sees progress being made and pharmacy gaining in its recognition and importance at a rapid rate. Much of this is due to improved leadership, but not a little is due to the efforts of all pharmacists, worthy of the name, to meet this challenge and to do so in a creditable way.

As long as pharmacy remains dynamic and looks to the future, refusing to live in the past, its place in the scheme of things will always be there. It is not change that we need fear but the forces of reaction that either refuse to acknowledge its inevitability or, worse, fight against all changes, even those admittedly good. Let those to whom the "new horizons" appear dark look more closely for the brilliance that lies beyond.

L. F. Tice

TRENDS IN MODERN MEDICINALS*

By Madeline O. Holland, D. Sc.**

A GREAT many stirring events have taken place in the world in the past two years. Both the European and Pacific Wars have ended and the world slowly and with great difficulty is attempting a readjustment to a peacetime status and philosophy.

Pharmacists and physicians now find their pharmacologic armamentarium greatly expanded with many new drugs of a highly specific nature and now available for civilian use. Many of these were developed under the intense program of war-time research. It is the purpose of this article to briefly review some of these new medicinals giving such pertinent data as seem indicated.

Influenza Virus Vaccine Types A and B

One of the many drugs to be developed as a result of research during the war period was the influenza virus vaccine. This vaccine is manufactured by inoculation of the virus into the allantoic cavity of chick embryos in ten-day old eggs, followed by incubation for forty-eight hours. The allantoic fluid is collected, centrifuged to separate the virus, dissolved and treated with formaldehyde. It is then tested for sterility and safety. The vaccine is employed for immunization against influenza particularly during epidemics.

Influenza is characterized clinically by a pathogenic effect upon the epithelium of the respiratory passages. The virus A type has an abrupt onset with fever and severe constitutional symptoms lasting three or four days. Its incubation period is from one to two days. Virus B influenza has a more gradual onset with less intense symptoms and a shorter duration of fever. The incubation period for this type is less than twenty-four hours. Influenza is spread readily from man to man and its care is symptomatic, supportive or preventive. The extreme debility caused by this disease is out of all proportion to the short duration of the acute stage of the disease. The economic waste of man hours is great.

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* Presented in part before the Connecticut Association for the Advancement of Professional Pharmacy, June 4, 1946.

** Managing Editor, *American Professional Pharmacist;* Technical Editor, *El Farmaceutico;* and Consultant.

The influenza virus vaccine was first tested in November and December of 1943 when a widespread epidemic occurred. The subjects selected included 12,500 A. S. T. P. men. Of these 6,211 remained unvaccinated and 6,263 were vaccinated. In the former the attack rate was 7.11 per cent and in the latter 2.22 per cent. The dosage of the vaccine is 1 cc. administered subcutaneously. The immunization lasts for a few months. Therefore, if it is desired for the entire winter, the vaccine must be administered every three months. The immunization may not completely protect every individual but it does reduce the likelihood of disease and the severity of the infection if contracted. There are no serious reactions to the vaccine itself although it is necessary to beware of possible hypersensitivity of the patient to the antigen or to egg protein. The patient may also have been previously sensitized by injections of vaccines prepared from chick embryos. Before administration the vaccine should be well shaken. It should be stored at a temperature of 36° to 50° F. since freezing destroys its potency. At the present time Influenza Virus Vaccine Types A and B is marketed by Eli Lilly, Parke-Davis and Co., Pitman-Moore and E. R. Squibb and Sons.

Digitoxin

The next drug to be considered is one which involves digitalis therapy which has been under scrutiny for so many years. Gold has stated that there are four significant factors in selecting a digitalis preparation. They are as follows: (1) potency; (2) absorption; (3) speed of action; and (4) speed of elimination. Digitalis itself does not possess all of these advantages. The assay of digitalis is dependent upon the intravenous injection of a preparation into cats. Results with this method are not altogether reliable in predicting the therapeutic effectiveness since digitalis varies in its absorbability when given orally. The ideal product would be one that is so well absorbed that oral and injected doses are the same. Furthermore, if it is rapidly absorbed from the gastrointestinal tract there is considerably less nausea and vomiting. Digitoxin offers these advantages as well as being more stable. It is standardized by weight and checked by assay on humans. Thus it obviates the problems of translating potency in animals to dosage in man.

Digitaline Nativelle is a similar product but is not identical. The original digitoxin was described by Schmiedeberg in 1875. The first

product of this nature to be made available was Purodigin and was presented by Wyeth, Inc. Other products now available are Digitoxin as marketed by Abbott and Squibb under that name, Cardigin by National Drug and Crystodigin by Eli Lilly. Digitoxin is a thousand times as potent as digitalis, therefore, 1 mgm. is the equivalent of 1 Gm. Sufficient digitoxin (1.2 mgm.) may be given at one time to digitalize the patient. An equivalent amount of digitalis to digitalize the patient at one time is not only unsafe but would also cause nausea. The maintenance dose of digitoxin is 0.2 mgm. daily.

Curare

Many of our present-day drugs have a romantic history. When we really delve into the background of these drugs we find that they are not so far removed from those that were used in ancient days. The Indians in South America used to employ an arrow poison which they prepared from the bark and stems of a plant. An infusion was first made and then concentrated to a syrup into which they dipped the tips of their arrows. In 1595 Sir Walter Raleigh brought some of this poison to England for investigational purposes but due to the limited supply no great discoveries were made.

In more recent years it was discovered that this tube curare contained an active principle known as d-tubocurarine chloride. This substance causes an interruption of the nerve impulse at the neuromuscular junction. The motor nerve impulse travels to the muscle where the contraction is mediated by acetylcholine. The curare principle neutralizes the acetylcholine reaction probably by the prevention of muscle acceptance of it. Thus the transmission of the impulses is intercepted. The degree of interruption depends upon the amount and the reaction is reversible in that normal activity is resumed as soon as the curare disappears.

In large doses curare causes paralysis and in smaller doses relaxation. It acts as an antidote to prostigmine. The uses of this drug are four, as follows: (1) as an adjunct to soften the convulsions of metrazol therapy; (2) to obtain complete muscular relaxation particularly in abdominal surgery and thus reduce the quantity of anesthetic required; (3) as a diagnostic agent in myasthenia gravis in that it worsens the condition; and (4) in the relief of spastic and athetoid states. It has been stated that curare has proved the greatest boon to schizophrenics who otherwise might not be able to withstand

the severity of shock therapy, curare acting to soften the convulsions. It is available under the trade name of Intocostrin and is manufactured by Squibb. Each cc. of the solution contains 20 mgm. of the drug.

Prostigmine

Prostigmine is not exactly a new drug but it is mentioned here because some new uses have been found for it. The action of prostigmine is similar to that of physostigmine (eserine) but is less toxic. It was first synthetically produced by Stedman in 1931 and has been used for the same purposes as eserine and related drugs. These uses include post-operative paresis of the bladder; relief of intestinal distention; and in the relief of intra-ocular pressure in glaucoma.

There are several new uses which have been established for prostigmine in therapy. As previously stated under curare, it acts directly opposite to curare and therefore the two are antidotes for each other. Since curare is used as a diagnostic agent for myasthenia gravis by worsening the condition it is logical to assume therefore that prostigmine should be of value in the treatment of this condition. It is administered either orally or parenterally. Employed as a therapeutic test for pregnancy, in the pregnant woman no effect is noticed but if there is no such condition it will bring on menstruation in a high percentage of cases. In infantile paralysis it reestablishes muscular coordination and makes muscle reeducation more easy by increasing the muscle response to nerve stimulation.

Stimulation of the parasympathetic nerves causes a release of acetylcholine which in turn affects the muscles. Acetylcholine is rapidly hydrolyzed by the enzyme cholinesterase but this enzyme is inhibited by such drugs as prostigmine and eserine. Thus the stimulus to the muscle is both intensified and prolonged by the inactivation of the cholinesterase. Prostigmine, manufactured by Hoffman-La Roche, is available as the methyl sulfate for parenteral use and as the bromide in the form of tablets for oral use.

Dental Caries

Surveys have revealed that persons drinking water with a high fluoride content develop mottled tooth enamel. However, they have found that such persons with this mottled enamel are less likely to have dental caries. Studies have been made by adding fluorides to the water of one town and using as a control a neighboring and simi-

lar town where no fluorides were added to the water supply. Noticeable results were obtained in these studies. However, it is difficult to control the human consumption of water in order that the individual may receive sufficient fluoride. Therefore it was felt that a dosage form was needed. Studies relative to this were conducted on children from eight to sixteen years of age. One group received no fluorides. The increase in the incidence of dental caries amounted to 40-65 per cent. In those children receiving fluorine (one p.p.m.) or calcium fluoride (3 mgm.) a 27 per cent increase was noted. In a third group given the fluoride plus vitamins C and D an increase of only 24 per cent was noted. Thus it can be seen that fluoride has some effect on the incidence of dental caries. A significant reduction is also noted when vitamins C and D are added.

The theory advanced for these observations is that the fluoride forms fluorapatite with the enamel of the teeth. This fluorapatite is harder and more resistant than calcium phosphate. There are three products now available for use in prevention of dental caries. They are as follows: Enziflur, marketed by Ayerst, McKenna and Harrison in the form of tablets which contain per tablet, calcium fluoride, 3 mgm., vitamin C, 30 mgm. and vitamin D, 400 units; Fluoros D, marketed by National Drug Company containing seven and one-half grains of bone meal (0.1 per cent fluoride), vitamin D, 400 units, calcium and phosphorus; Ce-De-Flor, marketed by Haack Brothers containing calcium fluoride, 3 mgm., vitamin C, 30 mgm. and vitamin D, 1000 units.

Sulfathalidine

The sulfonamide drugs have more or less taken second place in the attention of the world since the advent of the microbiotics. However, a new sulfonamide drug introduced some time ago for veterinary use has now found application in human illnesses. Phthalylsulfathiazole is a relatively nontoxic sulfonamide for the treatment of colon infections. It acts as an intestinal bacteriostatic agent. It can be maintained in high concentration in the intestinal tract where its bacteriostatic activity markedly alters the bacterial flora. Only 5 per cent is absorbed from the bowel. It is rapidly excreted by the kidneys. The free form is not excreted in very large quantities and the conjugated form forms soluble salts even at a pH of 5.6. No crystalluria is observed. Phthalylsulfathiazole is a white crystalline powder practically insoluble in water and weak acid. It is dissolved by an excess

of an aqueous solution of sodium bicarbonate or sodium carbonate with a release of carbon dioxide. Employed in the treatment of ulcerative colitis, regional ileitis, giardiasis, paratyphoid infections, and to supplement the therapy of amebiasis, it is also of value in intestinal surgery. Sharp and Dohme supply this drug under the brand name of Sulfathalidine, in 0.5 Gm. tablets.

Combisul

Although there have been very few new sulfonamide drugs brought to the fore recently, a new principle has been evolved. This principle involves the use of a combination of two sulfonamides wherein it has been found that each acts as if the other were absent except in their effect on bacteria. It has been noted that a saturated solution of one will dissolve as much of the other as will pure water. Combisul T D contains 0.25 Gm. each of sulfathiazole and sulfadiazine. It has been found that such a combination reduces considerably renal damage and crystalluria. With sulfathiazole alone crystalluria occurs in 70 per cent of the cases and with sulfadiazine in 29 per cent of the cases. When the two drugs are combined it occurs in only 7 per cent. Renal toxicity occurs in 3 to 5 per cent of the cases when either drug is used alone but in the combination it is reduced to zero. Drug fever occurs with sulfathiazole in 10 per cent of the cases and with sulfadiazine in 2.4 per cent. In the combined form drug fever is observed in only 1.4 per cent. Combisul D M contains sulfadiazine and sulfamerazine, of each 0.25 Gm. The T D is used successfully in pneumonia, respiratory and other related infections. The D M is employed in meningitis. The dosage given is the same as with a single sulfonamide. The initial dosage is 4 Gm. followed by 1 Gm. every four hours. Adjuvant measures of alkalization and forcing of fluids may be omitted but patients should not be deprived of this added protection if needed. All other precautions with sulfonamide drugs should be observed.

Folic Acid

The complex nature of the B vitamins has been known for some time and several of the factors have been isolated. However, in administering these factors to chicks it was noted that a severe anemia developed when the individual factors were administered rather than the entire food material. This factor was found to be present in

liver, yeast and alfalfa. It was subsequently called vitamin Bc or factor U. During this period certain workers found that another factor was necessary for the growth of the lactic acid organism, *Lactobacillus casei.* This was called the *L. casei* factor. It, too, was found to have some relation to this anemia factor.

An anemia in monkeys was found to occur when a certain factor was absent. This was called vitamin or factor M. Finally, the vitamins Bc and M were determined to be the same factor as found in green leaves in minute amounts. It was therefore named folic acid. Since that time it has been synthesized and has been found equal to liver extract in macrocytic anemias such as pernicious anemia and those occurring in sprue, pellagra, and pregnancy. Macrocytic anemias are characterized by too few and abnormally large red cells and are usually caused by nutritional deficiencies. Folic acid has been found to be orally effective in such anemias. It is particularly valuable in patients who are sensitive or who have developed a sensitivity to liver extract.

The outstanding observation relative to this compound is the fact that a synthetic nutritional factor has been found to stimulate red cell formation. Folic acid has been found to be a specific in the problem of large cell anemias and by finding a single synthetic substance it has been observed that complex physiological reactions are not necessary. Folic acid is now available in 5 mgm. tablets under the brand name of Folvite and is marketed by Lederle Laboratories.

Antimalarials

It is almost impossible to believe that 25 per cent of the inhabitants of the globe have malaria. A great deal of work has been done on antimalarials and an extensive research program was carried out during the war years as prompted by the exigencies of the times. The ideal antimalarial would be one that prevents relapses. In recent months there has been considerable publicity on a new antimalarial first called SN7618 and now given the name chloroquine by the Council on Pharmacy and Chemistry of the American Medical Association.

Chloroquine is superior to atabrine for the following reasons: (1) It causes an abrupt termination of the clinical attack of vivax malaria (non-fatal, up to twenty relapses in three years) and will cure falciparum malaria (often fatal, but not relapsing) when administered for only one to two days as compared with four to six days for

atabrine. (2) It is an effective suppressive (keeps disease mild or dormant) when administered no more frequently than once weekly in a well-tolerated dose. The once-a-week dosage is less than one-half the total amount of atabrine that must be consumed in a week. (3) It does not discolor the skin as does atabrine. (4) It does not produce the disagreeable gastrointestinal symptoms which are sometimes encountered with atabrine. (5) The cost of production is the same as for atabrine. Chloroquine or SN7618 has been successfully used in 5000 human cases of malaria including more than 1000 in the Armed Forces. The dosage of this drug as would be used in the suppression of malaria is 0.3 Gm. given weekly and on the same day each week. For treatment of a case of malaria the initial dose is 0.6 Gm. followed by 0.3 Gm. six to eight hours later and 0.3 Gm. on each of two consecutive days. A dosage of 1.2 Gm. in divided doses may be administered for twenty-four hours. In a comparative study with quinine and atabrine relapses were found to occur in 40 per cent of the cases treated with quinine; in 26 per cent with those treated with atabrine; and in 21 per cent with those treated with chloroquine. Chloroquine is available as Aralen from the Winthrop Chemical Company.

British workers recently announced a new and more effective synthetic chemical substance for malaria known as paludrine. Chemically this drug is known as N_1-p-chlorophenyl-N_3-isopropylbiguanide. This drug appears to have advantages over both quinine and quinacrine (atabrine). It is less toxic than either, which means it can safely be administered over a long period without risk of untoward reactions or after-effects. It appears to be effective in preventing relapses of benign tertian malaria; one of the commonest forms of malaria, for which other drugs are almost useless in cases of relapse. It is more powerful and the equivalent dose is found to be one part of paludrine equal to three of quinacrine (atabrine) or to ten of quinine. Quinine and quinacrine have shown themselves most effective in controlling the worst symptoms of malaria, but all the parasites are not destroyed. Later when the sufferer ceases to take the drug, he frequently falls again with an attack.

Another advantage that paludrine possesses over quinacrine is that it does not produce the yellowing of the skin characteristic of the person who has been taking the latter. Its prophylactic action is also greater. Although more prolonged trials are required, the new drug

may afford almost 100 per cent protection if taken in the correct doses.

The most recent antimalarial to be announced is SN13,276. This drug possesses possibilities of curing vivax or relapsing malaria. However, the clinical trials are as yet too incomplete to say definitely.

Rh Factor

The existence of different blood types has been known for many years. One classification used today is as follows:

Type		Per Cent of Population
O	No agglutinogens in cells A and B agglutinins in serum (universal donor)	45 per cent
A	A agglutinogens in cells B agglutinins in serum	41 per cent
B	B agglutinogens in cells A agglutinins in serum	10 per cent
AB	A and B agglutinogens in cells No agglutinins in serum (universal recipient)	4 per cent

Unfortunately, this classification does not take into consideration another agglutinogen which is present in 85 per cent of humans (whites). In 1940 Landsteiner and Wiener injected the blood of rhesus monkeys into rabbits thus developing agglutinins in the rabbit serum that would clump monkey cells. This same rabbit serum clumped the cells of 85 per cent of humans regardless of the blood group shown above.

The agglutinogen responsible for this clumping has been called the Rh factor taken from the word rhesus. As stated previously it is present in 85 per cent of humans. In other words 85 per cent are Rh+ and 15 per cent are Rh—. It is a dominant hereditary trait and can cause a great deal of trouble in transfusions. The transfusion of Rh+ blood into an Rh— individual results in iso-immunization so that antibodies (agglutinins) form which will clump any successive transfusion of Rh+ blood.

If a woman who is Rh— marries a man who is Rh+ and in due time becomes pregnant the foetus will be Rh+. If there is some

damage to the membrane between the foetus and the mother, some of the foetal blood will seep into the mother forming agglutinins which in turn pass back into the foetus and clump the cells causing the condition known as *erythroblastosis fetalis*. This is most likely to occur in successive pregnancies. If the baby survives it is possible to overcome the condition with a transfusion of Rh— blood. The mother's blood must not be used even though it is Rh— since it possesses the agglutinins. The father's cannot be used because it possesses the Rh agglutinogens.

In emergency transfusions when there is not time for blood typing, the O type or universal donor blood which is in addition Rh— should be used. Lederle Laboratories have recently made available an anti-Rh serum which is used for Rh typing. The serum causes Rh+ blood to clump. This can be examined macroscopically and there are very few cases of Rh+ blood which will not clump with this serum.

Motion Sickness

One of the most common conditions from which human beings suffer is known as motion sickness due to train, airplane or boat travel. In the past the barbiturates have been used but have not proven very effective. A new product known as Vasano and marketed by Schering which contains 0.4 mgm. of hyoscyamine camphorate and 0.1 mgm. of scopolamine (hyoscine) camphorate in tablet form has been found successful. However, with all these remedies there is one disadvantage in that they produce drowsiness. This is of no significance in regards to passengers but it is quite significant if taken by pilots.

Promin

Leprosy has been a long-treated disease and one for which very little effective therapy has been developed. A new drug, promin, recently placed on the market and known chemically as sodium p,p′—diamino—diphenyl—sulfone—N,N′—di—(dextrose sodium sulfonate) has proven of some value in leprosy. It is intravenously administered in doses of 2 to 5 Gm. (5-12.5 cc.) daily for six consecutive days and omitted on the seventh day. At the conclusion of each four months of treatment it should be interrupted for a period of one or two weeks. Serious toxic reactions from this drug are rare although a slow destruction of red cells has been observed. The patient should be kept under constant observation and complete blood counts done

every two weeks. This chemical is not a specific but it does have a slow definite action.

Experiments were carried out at the Carville leprosarium which showed that any drug expected to be bactericidal against *M. leprae* will be slow, as the disease attacks the skin and the peripheral nervous system, which are difficult of access by blood. *M. leprae* is a wax-encapsulated, resistant organism, and found more abundantly in lesions than is customary of other infections. Incubation periods for leprosy are long, requiring years for development. Most of the experiment's subjects had suffered from the disease for a number of years. Despite all of these deterrents to chemotherapeutic action, promin showed noteworthy value against leprosy. Promin ampuls containing 2 Gm. of the substance are available from Parke Davis. Promin jelly is used topically in tuberculous lesions.

Furacin

There has been developed recently a synthetic compound chemically known as 5—nitro—2—furaldehyde semicarbazone. This compound occurs in the form of bright yellow crystals and is soluble in various solvents as follows: water, 1:4200 Gm./cc.; alcohol (95%), 1:590 Gm./cc.; acetone, 1:415 Gm./cc.; ether, 1:12,500 Gm./cc.; benzene, 1:43,500 Gm./cc.; chloroform, 1:27,000 Gm./cc.; propylene glycol, 1:300 Gm./cc.; carbowax 1500, 1:100 Gm./cc. It is a nontoxic and nonirritating compound with a low index of sensitization. It has been made available as Furacin Soluble Dressing by Eaton Laboratories. The base of this soluble dressing is water washable and water miscible and can be removed from wounds with warm or cold water or physiological saline solution. The base mixes with body fluids readily releasing the furacin. It does not retard tissue repair. It is composed of carbowax 1500, 55 per cent; carbowax 4000, 20 per cent and propylene glycol, 25 per cent. Furacin soluble dressing is used as a local application to kill bacteria without too much injury to human tissues. It is effective in old wounds and in the presence of blood, pus, serum, serous exudates and bacterial debris. It is employed in the following special conditions: surgery—infected surface wounds; severely infected burned areas—third and fourth degree burns; varicose ulcers; carbuncles and furuncles, after surgical intervention; superficial ulcers of diabetics; and areas being prepared for skin grafting. Pediatrics—impetigo of infants and children; sec-

ondarily-infected eczema. Dermatology—impetigo of adults and children; secondary infection of toes and feet superimposed on a fungus infection. Secondarily-infected eczema—orthopedic surgery; areas being prepared for skin grafting; osteomyelitis associated with compound fracture. Routine dressing for non-infected wounds—minor lacerations; abrasions; avulsed wounds.

The dressing may be placed directly on the wound, with or without covering with a dry dressing. Limited quantities may be melted and poured into the wound or it may be placed on gauze, which is then applied and covered with a bandage. The dressing may be changed one to three times every twenty-four hours. There may be a slight liquefaction on the surface of this dressing in hot weather. For this reason it should be stored in a cool place.

Fertility

A recently developed product for the promotion of fertility has been made available by Ortho Pharmaceutical Company. This product known as Nutrisal contains potassium chloride, sodium chloride, calcium gluconate and glucose. It provides glucose in modified Ringer's solution. As a vaginal douche when dissolved in water, it aids in the survival and migration of sperm thus promoting the likelihood of fertilization where no serious condition causing infertility exists.

Migraine

Migraine has been a subject of discussion for many, many years. Included in this syndrome are periodic headaches, nausea and vomiting. Ergotamine tartrate has been used in the treatment of migraine. A new drug recently made available by Sandoz Pharmaceutical Company and known as dihydroergotamine has been found just as effective as the former. It causes paralysis of the sympathetic nervous system similar to that caused by ergotamine tartrate but it is eight to ten times less toxic. It differs from ergotamine tartrate in that it possesses no uterine effect even in large doses and possesses a less powerful vasoconstrictor action. It is a safe drug in avoiding acute attacks of headache but unfortunately it does not prevent recurrences.

Antispasmodic

A new antispasmodic for the urinary tract chemically known as 3-(beta-diethylaminoethyl) 3-phenyl-2-benzofuranone hydrochloride

has been recently developed. This drug acts as an antispasmodic on smooth muscle especially the kidney, ureter and bladder. It is employed to relieve spasm and pain caused by urinary tract calculi, catheterization injection of urinary contrast media and indwelling catheters or packs. It possesses marked local anesthetic properties particularly in the cornea on which it acts within thirty to eighty minutes but it produces considerable irritation. The side effects of this drug are less than with atropine. In urinary calculi, catheterization and similar cases the dosage is 100 mgm. intramuscularly. In bladder spasm the dosage is 50 to 100 mgm. orally. There may be some reactions following administration but a small quantity of barbiturate lessens them. It should never be administered intravenously since this brings the entire dose into the circulation at one time. This synthetic drug is available under the name of Amethone and is supplied in capsules and solution by Abbott Laboratories.

Two new antispasmodics have been developed which are not yet available for use. The two compounds being investigated by Frederick Stearns and Company are known as "Stearns 600" and "Stearns 606," or chemically as beta-diethylaminoethyl phenyl-alpha-thienylglycolate hydrochloride and beta-diethylaminoethyl phenyl-alpha-thienylacelate hydrochloride respectively. Both 600 and 606 are effective in reducing uterine irritability and the pain of dysmenorrhea. The former acts as a stimulant to the central nervous system whereas the latter does not. Thus it is probable that the latter is preferable since it relieves spasms and pain without excess nervous stimulation.

Anticonvulsant

Various drugs have been used through the years in the treatment of epilepsy. Some have been fairly successful, others of very little value. Abbott Laboratories have recently introduced a new drug under the name of Tridione. Chemically, this drug is 3,5,5 trimethyloxyazolidine 2,4 dione. This acts as an anticonvulsant in petit mal, myoclonic and akinetic seizures of epilepsy. It also acts as an analgesic. It is available in capsules or the capsules may be emptied and the powder mixed with milk or water for children. The elixir which contains 300 mgm. per fluid ounce is also employed. For injection purposes there is supplied a solution with 0.75 Gm. of urethane and 9.5 per cent of alcohol. This may be administered intravenously, intramuscularly or subcutaneously. A few side effects such as

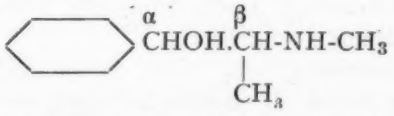
dermatitis have been noticed with this drug. The main side effect in adults has been photophobia, that is, a sensitivity of the eyes to bright daylight.

Fatigue

Fatigue is a rather usual condition experienced by most people in these hectic times. When a person is suffering from fatigue he secretes excessively large quantities of hormones produced by the adrenal gland. These hormones known as steroids are essential to life and similar chemically to the sex hormones. These steroids are subsequently excreted in the urine as 17-ketosteroids. There is a definite relationship, therefore, between the output of these 17-ketosteroids and fatigue. A synthetic compound has recently been developed which, when given orally, appears to be absorbed and transformed in the body into a variety of hormonally active steroid substances. It is nontoxic and in 50 mgm. doses is said to increase efficiency and lessen fatigue without noticeable harm. The individual taking this drug feels just as fresh at the end of the day as he would at the beginning. However, it does not take effect until after the third day. It also requires competitive activity. In other words if the individual has no incentive the compound will not have any effect. This compound is known as Δ_5 pregnenelone and is being studied for future release by Schering.

Sympathomimetic Drugs

A sympathomimetic drug is described as one which produces a rise of arterial blood pressure, dilatation of the pupil and contraction of the plain muscle of the orbit, flow of saliva and tears, and inhibition of the tone and rhythm of muscular walls of mammalian intestine. A number of such drugs have been developed and used in the past. They include such drugs as ephedrine and amphetamine. Natural ephedrine (*l*-ephedrine) is a laevo rotatory base in alcohol solution and has the formula:



It has two centers of asymmetry as designated by the carbon atoms marked α and β above. There also occurs naturally in certain other species of Ephedra a stereoisomeride of ephedrine known as *l*-pseudo-

ephedrine (*l* ψ ephedrine). This substance differs from true ephedrine only in the spatial arrangements of the substituent groups on the asymmetric carbons. Where the spatial arrangement of the substituent groups of both α and β carbons are reversed the corresponding enantimorph (mirror image) results, known as *d*-ephedrine and *d* ψ ephedrine respectively.

In the case of desoxyephedrine or deoxyephedrine, as it is sometimes called, the absence of oxygen in the structure results in only one center of asymmetry and thus there are the *d*-desoxyephedrine and its mirror image *l*-desoxyephedrine and the racemic mixture *dl*-desoxyephedrine. Desoxyephedrine was first prepared by Ogata in 1919 as *d*-desoxyephedrine hydrochloride which he called *d*-phenylisopropylmethylamine hydrochloride. Emde some years later, by the catalytic reduction of *d*-pseudo ephedrine, obtained *l*-desoxyephedrine and thus proved the structure of the ephedrine molecule.

A number of synonyms or proprietary names for the desoxyephedrines have been employed. Thus as other chemical names we have phenylisopropylmethylamine, N-methyl phenylisopropylamine, N-methyl amphetamine, N-methyl benzedrine and methylisomyn. These names can be understood from the chemical structures below wherein amphetamine is seen to be a lower homologue of desoxyephedrine differing from it only by CH_2 in total chemical constitution.

ephedrine

$C_6H_5CHOH\ CH\ (CH_3)\ NH\ (CH_3)$

desoxyephedrine

$C_6H_5CH_2CH(CH_3)NH(CH_3)$

amphetamine

$C_6H_5CH_2CH(CH_3)\ NH_2$

The dextro-rotatory form of desoxyephedrine is sold in Germany as "Pervitin" and in the United States and England as "Methedrine." The racemic form is available in the United States as "Oxydrene." Dexedrine, marketed by Smith, Kline and French Laboratories, is dextro amphetamine (benzedrine).

Desoxyephedrine is used in the symptomatic treatment of depressive mental states. It elevates the mood and counteracts sleepiness and fatigue. However, its effect decreases due to an accumulated need for rest. It has been recommended for use for railroad engineers, the personnel of motorized units, persons taking long automo-

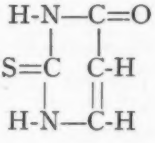
bile drives, night watchmen and the like. Where emergency conditions warrant its use, it can be used as a mental stimulant.

It is also quite useful in elevating the mood of persons who are in a depressed state following an operation or in those suffering from chronic disease or inoperable tumor. It is also employed in conditions for which amphetamine sulfate has been used such as narcolepsy, postencephalitic Parkinson's syndrome, chronic alcoholism, migraine and hay fever.

The most effective doses of this drug range between 2 and 6 mgm. If the dose is on the higher side there may be side reactions. Its effect is experienced in ten to twenty minutes after oral administration. Desoxyephedrine also possesses a vasoconstrictor action when applied topically. When used alone on the nasal mucosa a concentration of 1 per cent or more is necessary. It has been shown by Turnbull and his colleagues that a combination of desoxyephedrine and sodium sulfathiazole results in a synergism which in turn causes a greater degree of vasoconstriction. It is believed that a new compound known as desoxyephedronium sulfathiazole is formed. A number of proprietary preparations are now marketed combining 2.5 per cent of sodium sulfathiazole, sesquihydrate and 0.125 per cent *dl*-desoxyephedrine hydrochloride. Anhydrous sodium sulfite 2 per cent is added as a preservative. Some of these drugs now available on the market are: Squibb's Sulmefrin, Abbotts' Sulfedex, Parke-Davis' Sulfamone and Lilly's Thizodrin. A similar product containing 1 per cent of sodium sulfathiazole and 1/10 per cent *dl*-desoxyephedrine hydrochloride is employed in epidemic conjunctivitis. It lessens the congestion causing vasoconstriction.

Hyperthyroidism

Several years ago it was noted that rape seed contained a goitrogenic principle. When extracted and analyzed this principle was found to be a derivative of thiourea. Further studies of thiourea revealed a compound which was a heterocyclic derivative and was called thiouracil. Its clinical formula is 2-mercapto-4-hydroxypyrimidine. Structurally it is as follows:



Thyrotoxicosis is that condition which occurs when an over-function of the thyroid gland in the body causes an excessive amount of thyroid hormone (thyroxin) to be produced and released. This is manifested by an increased metabolic rate; various nervous effects; loss of weight; sometimes an increased pulse rate; and other symptoms. In many cases the condition is not serious enough to require hospitalization but when the condition becomes too serious the only therapy available has been subtotal surgical resection of the gland or partial removal. Such a condition makes a patient a poor surgical risk due to the high metabolic rate. Thiouracil when administered lowers the metabolic rate to normal levels, causes return to normal of the protein-bound iodine of the plasma and concurrently a clinical remission of the disease. Therefore, this drug is employed preoperatively or in place of surgery.

It is contraindicated in pregnancy and lactation since it passes through the placental barrier. It is to be given under strict control and on prescription only, with a warning label as to the possible side effects. The principle side effects which have been observed were most all due to drug allergy. This drug has one drawback in that it sometimes causes agranulocytosis. Thiouracil is available under that name from Abbott Laboratories, Eli Lilly and Co., E. R. Squibb and Sons, William H. Rorer and Winthrop Chemical Co. Lederle Laboratories have named their thiouracil, Deracil.

There have been reported hyperthyroid patients who have not responded to other forms of treatment or who have been sensitive to iodine or thiouracil.

Roentgen treatment as well as ordinary iodine by mouth have been used in treating hyperthyroidism for many years with some success. With the introduction of radioactive isotopes of iodine it was thought that the beta rays from iodine if rendered radioactive, would provide a greater radiation effect than that furnished by Roentgen rays which had to pass through the skin and tissues, since the thyroid gland does selectively absorb iodine. Consequently, studies were begun on the use of radioactive iodine. Clinical trial has shown that therapy with radioactive iodine is of value. The radioactive iodine is administered orally in about 1 mgm. or less in ordinary iodine. The radioactive iodine is found to concentrate mainly in the thyroid gland. The beta rays furnish an internal radiation similar physically to Roentgen radiation.

The radioactive iodine is prepared by the nuclear bombardment of metallic tellurium which transmutes tellurium into iodine. The radioactive iodine is then separated from the target by adding to the metallic tellurium 0.5 mgm. of iodine as potassium iodide and 25 cc. of three molar sulfuric acid. The solution is heated while adding concentrated nitric acid a drop at a time. Thus, the target is dissolved and the iodine distilled over as elementary iodine and collected in carbon tetrachloride. The carbon tetrachloride solution is washed once with water in a separatory funnel, the iodine reduced with sodium bisulfite and extracted in an aqueous layer as sodium iodide. The aqueous solution is then filtered to remove any droplets of tetrachloride. The preparation is administered to the patient within one to four hours after the bombardment because of the rapid deterioration. The solution as administered to the patient is distilled water containing fourteen to seventy-nine millicuries (a millicurie is 37,000,000 atoms disintegrating per second) of twelve-hour iodine and approximately one-tenth of that quantity of eight-day iodine in 0.5 mgm. of iodine as sodium iodide.

Dermatophytosis

Dermatophytosis, or dermatomycosis, is defined as any disease caused by a parasitic plant growth. Although this condition was receiving increasing attention in medicine prior to the War, fresh significance accrued when the United States was drawn into the conflict. War, marching soldiers, and their feet are inseparable problems. A survey revealed that no less than 8 per cent (one in every twelve) of all hospital admissions in the Armed Forces were for cutaneous disease. Dermatophytosis ranked second on the list.

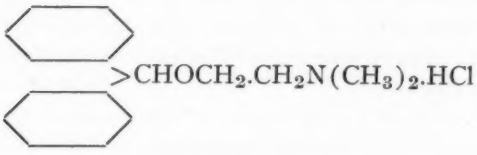
The American Medical Association has established certain maxims for prophylaxis and treatment of dermatophytosis (athlete's foot) which everyone would do well to follow and pharmacists would do well to publicize to their patrons. Several new products have recently been developed and marketed which have been of value in the treatment of dermatophytosis. Sopronol is marketed by Wyeth, Inc. This product contains sodium proprionate and is available in the form of an ointment, a powder and a liquid. Propionic acid and the propionates have been found of greater value in the treatment of dermatophytosis, not only of the feet but also of the groin and other portions of the body. Sodium propionate is available under the name

of Mycoban from E. I. duPont de Nemours and Co., Wilmington, Delaware.

Desenex, as marketed by Wallace and Tiernan Products, Inc., contains undecylenic acid and zinc undecylenate in ointment and powder form. These products, too, have been found of value in the treatment of dermatophytoses.

Allergies

The subject of allergies, particularly to the spring pollens and the ragweed, have been a matter of controversy for many years. No cure has been found for these conditions. A new drug, recently released, chemically is beta dimethylaminoethyl benzyhydryl ether hydrochloride and is sold by Parke Davis as Benadryl. Its structure is



It acts as an antispasmodic and an antihistamine substance. It is a white crystalline powder forming a slightly opalescent solution. It is soluble in water and alcohol and stable under ordinary conditions of temperature and pressure. It possesses three significant actions as observed on animals; (1) it alleviates the bronchial constriction caused by histaminic or anaphylactic shock; (2) it counteracts the vasodepressor effects of histamine; and (3) relieves the spasm of smooth muscle. Many of these symptoms of anaphylactic or allergic reactions are believed due to the liberation of histamine. It is thought, therefore, that the therapeutic efficacy of Benadryl in allergic conditions could be due in large measure to interference with the action of histamine. It is believed that Benadryl acts by being adsorbed onto the site of action of histamine and thus histamine has less opportunity to reach and combine with its site of action. There is apparently a competition between the two substances. Benadryl is indicated in the treatment of edema problems having as a common etiologic agent the release of histamine or histamine-like substances. In urticaria it relieves the condition but does not cure it. It has also been employed with success in high fever serum-sickness, pylorospasm, spastic colitis, dysmenor-

rhea and in the physical allergy of the head syndrome which includes perennial vasomotor rhinitis, myalgia, Meniere's disease, and vasodilating pain. It has been employed in bronchial asthma but has not been found very effective. In children it has been employed in the treatment of hay-fever, asthma, vasomotor rhinitis, urticaria and serum reactions. The main side reactions encountered with this drug are sleepiness, dizziness, dry mouth and a feeling of nervousness, all of which passed very quickly. The sleepiness at night is not too objectionable in hay-fever patients since they usually have difficulty in sleeping. Amphetamine administered during the day with the Benadryl has been found to overcome this side-effect. A possibility of a use for Benadryl in gastric acidity has been advanced. Histamine increases gastric acidity. Benadryl depresses this gastric response to histamine and thus may some day prove to be a new factor in the control of gastric acidity. The dose of Benadryl is 50 mgm. three or four times a day. Where a persistent narcotic effect is noticed, smaller doses should be given. The effect lasts from five to eight hours. It is available in capsules and as the elixir.

Anthallan, known chemically as the lactone of beta-gallic acid-ethanol-alpha-di (N-butyl) amine, is derived from the aminized phthalides. It is made available by the Medico Chemical Corporation of America and is indicated in nonseasonal hyperesthetic rhinitis, urticaria, papular urticaria and neuro-dermatitis disseminata. It is administered in doses of three to twelve capsules (0.085 Gm. each) daily. It appears safe for human use since its toxicity is extremely low. Excellent results are claimed to have been obtained in a high percentage of cases of seasonal and non-seasonal hyperesthetic rhinitis in the few cases reported so far in the medical literature, but further clinical study seems indicated.

Amino Acids

The subject of amino acids is a very lengthy one which will be dealt with briefly, in this review. An essential amino acid is defined as one which cannot be synthesized by the animal body at a rate commensurate to meet its needs for normal growth. Certain amino acids are essential for growth, maintenance and physiologic well being. Those found by various workers including Rose to be essential for the rat are:

Essential	*Non-essential*
lysine	glycine
tryptophan	alanine
histidine	serine
phenylalanine	norleucine
leucine	aspartic acid
isoleucine	glutamic acid
threonine	hydroxyglutamic acid
methionine	proline
valine	hydroxyproline
arginine	citruline
	tyrosine
	cystine

In humans only eight are essential, histidine and arginine being in the non-essential list. It must be understood, of course, that the non-essential amino acids are not necessarily unused by the body, but they are the ones which the body itself, can, if required, manufacture. Amino acid therapy is indicated for the optimal growth and tissue repair in health as well as in disease. It is indicated in hypoproteinemia of nephrosis, nephritis, neoplastic diseases, ulcerative colitis, hyperthyroidism, hepatic insufficiencies; in anemia; pregnancy and lactation; burns; ulcers; kidney diseases; preoperatively and postoperatively to protect the liver from the damaging effects of anesthetics; and in reducing the postoperative loss of nitrogen. It must be remembered that the amino acids are not a substitute for blood, serum or plasma transfusions in acute severe hypoproteinemia and shock.

The amino acids products on the market are available for oral and for parenteral use. Arlington's Aminoids are a granular powder for oral administration. Parenamine, marketed by Frederick Stearns is a 15 per cent solution for parenteral administration. Mead Johnson's Amigen is marketed as the powder for oral use and in a 5 per cent solution with 5 per cent dextrose for parenteral administration. Nutramigen is also a powder and contains other substances such as olive oil, starch, calcium gluconate, dextri-maltose, yeast and mineral salts. National Drug has made available three products which are known as Aminonat, Aminovite and Amiron. The first two mentioned are powders and the third is a liquid. Aminovite contains

vitamins and minerals and Amiron contains vitamins and iron. Lactamin is also a powdered protein hydrolysate being manufactured by Wyeth, Inc. Sharp and Dohme has recently made available Delcos Granules which is not a protein hydrolysate but simply a protein concentrate.

Co Tui has done a great deal of work on the amino acids. Among his studies was evolved a new treatment for peptic ulcers. The amino acids were administered to patients suffering from peptic ulcers. The results observed include a cessation of pain and distress and vomiting. A positive nitrogen balance was established and a gain in weight, strength and morale occurred. One might ask at this point just how this works. The amino acids are amphoteric substances and the addition of these substances to a hyperacidic gastric juice raises the pH to almost the point of abolition of peptic activity. The pH of gastric juice originally between 1.92 and 2.05 was raised by amino acids to 4.24. The free acid present was reduced to zero for about an hour and fifteen minutes. After that the pH again began to drop and the free acid to rise. It is believed that healing in these cases is aided by this neutralization of the acid along with the providing of a rich nutrient solution to enable the body to build up its tissue deficiency.

Wyeth, Inc., has just recently released a product known as Meonine in the form of crystals and tablets. This, the amino acid methionine, is a specific for the prevention and repair of liver damage associated with many clinical conditions and toxic damage produced by such poisons as carbon tetrachloride.

Controlling Bleeding in Surgery

The Upjohn Company have recently made available materials for a new technic for surgical hemostasis. These materials are known as Gelfoam and Sterile dried beef thrombin. The study of the coagulation mechanism of the blood has resulted in the production of clotting without injuring the surrounding tissue. Clotting of blood can be conceived of as taking place in three steps as follows:

I. Thromboplastin is released from injured tissue cells and from blood platelets when the latter come in contact with a foreign surface.

II. Thrombin is formed by the reaction:
Thromboplastin + Calcium ions + Prothrombin → Thrombin

III. Fibrin is formed by the reaction:
Thrombin + Fibrinogen → Fibrin

The end result of the first two steps of this process is thrombin which directly converts fibrinogen to fibrin. Therefore, application of thrombin to the bleeding point will cause clotting promptly. One of the difficulties of using the thrombin solution as a hemostatic is the necessity for using in conjunction with it an absorbent material such as cotton. When bleeding occurs in a wound that must be closed it is necessary to remove the cotton but the clot is very often removed with it and bleeding is again started. For this purpose a sponge-like material known as fibrin foam was prepared from human fibrin. It could be saturated with the thrombin solution, applied to the sight of hemorrhage and allowed to remain there after closing the wound since it was readily absorbed by the tissues. Unfortunately, only moderate supplies of both fibrin foam and thrombin made from human blood have been made available. For this reason research was conducted to develop Gelfoam and thrombin from animal sources. Gelfoam is a spongy substance of partially denatured gelatin that has proven not only as satisfactory as fibrin foam, but in a number of respects actually superior to it. It is a glistening white porous mass that when dry can easily be cut into any desired shape with a sharp knife. When moistened with thrombin solution it becomes absorbent and pliable; wet, it adheres readily to the bleeding area, forming, after it is held in place for a few moments, an actual patch on the injured surface.

Of special interest and importance is the fact that the absorbent properties of Gelfoam cause it, when it is applied to a bleeding surface, to soak the blood into its own interstices so that the clot formed is largely in the Gelfoam. Thus no thrombin spreads into the opened vessels and thrombosis does not occur.

Gelfoam is readily absorbed by the tissues and does not cause any excessive inflammatory action. The thrombin is beef thrombin and its repeated use in man as an hemostatic agent fails to produce detectable antibodies and in practice has never caused sensitization, agglutination or other unfavorable reactions. Although the usefulness of these two substances is not limited to neurosurgery they have been used more extensively in this field at the present.

After several years of intensive research Johnson and Johnson investigators have developed a hemostatic agent to control bleeding during surgical operations.

The new product, to be known as "Hemo-pak" when available commercially, is derived from a raw material called alginic acid extracted from seaweed. It will be produced in a gauze-like form and may be left in the body and the patient sewed up, after which the hemostatic agent is ultimately absorbed and carried away by the tissue fluids.

Soluble cellulose has also been suggested as a hemostatic agent. Lederle Laboratories and Parke-Davis and Company have done considerable work on this material. The oxidized cellulose disappears readily in the tissues without tissue reaction. It may be used also as a carrying material for thrombin in cerebral surgery.

Rutin

A drug with medical values undetected for more than a century, is ready for full scale production for the first time and enough to meet present medical needs in treating fragile and weakened capillaries will be available this year.

Commercial manufacture of rutin, a bright yellow non-toxic powder, has been made possible by the discovery by the Bureau of Agricultural and Industrial Chemistry that the green buckwheat plant is an economical source.

According to clinical observations at the Medical School of the University of Pennsylvania, rutin is effective in the treatment of conditions arising from high blood pressure associated with increased capillary fragility. Bursting of weakened blood vessels causes small hemorrhages which may result, when the rupture occurs in the eye or brain, in blindness or apoplexy.

Research indicates also that rutin, a glucoside, may have equally unsuspected nutritional values. Further investigation of the nutritional uses is expected, but the studies point to the opinion that rutin could serve the circulatory system in a manner resembling the action of vitamin C in the growth and hardness of teeth and bones.

Adrenochrome

An oxidation product of adrenalin known as adrenochrome has been found in Germany and brought to the United States. Adreno-

chrome is an important tool in testing certain modern theories of the causation and possible therapy of hypertension. It has been tested only on laboratory animals. It is thought that adrenochrome itself has little future as a therapeutic agent, but that good results may be obtained with some of its derivatives.

Carbon 13

A great deal has been heard about atomic fission. The Sun Oil Company and the Houdry Process Corp. with the aid of certain distinguished scientists, some of whom worked on the atomic bomb, have developed a new isotope known as Carbon 13.

This substance will probably rank in importance with x-ray as a tool of medical science. It makes it possible for the chemist to see and follow chemical reactions in the body. Carbon 13 is used as a tracer in probing the secrets of the fundamental processes that occur in all living things, as well as metabolic disease processes, of which cancer, diabetes, hardening of the arteries and so-called heart trouble are examples.

Indistinguishable chemically from ordinary carbon, Carbon 13 is absorbed in living tissues and undergoes the same metabolic process as does ordinary carbon. But where ordinary carbon cannot be traced as it passes through these intricate chemical reactions, which are the processes of life itself, Carbon 13 can be detected by the aid of an electrical instrument called the mass-spectrometer, and identified with specific bodily functions.

Microbiotics

A great many advances have been made in the microbiotics in the past year. Bacitracin was recently isolated from a strain of *B. subtilis*. It was first observed following studies of the bacterial flora of contaminated civilian wounds.

Direct blood agar plating of the injured tissue revealed organisms which did not show in broth cultures. They occurred most frequently when broth cultures contained certain sporulating Gram-positive rods. This antibiotic agent was found to be neutral, non-toxic and water soluble. Tests have shown that it may prove to be a valuable agent in the treatment of gas gangrene, gonorrhea and meningitis as well as hemolytic streptococcal infections.

Streptomycin has recently been released for limited civilian use. Much remains to be learned concerning limitations of streptomycin's usefulness, methods of administration, dosage and toxicity.

Studies are being carried out on the following list of diseases in which streptomycin has shown some promise:

1. Gram-negative bacillary infections of the genito-urinary tract resistant to the sulfonamides.
2. Gram-negative bacillary infections with bacteremia.
3. Hemophilus influenzae infections, including meningitis, pneumonia, middle ear disease and laryngotracheitis.
4. Friedlander's bacillus (Klebsiella pneumoniae) pneumonia.
5. Typhoid.
6. Salmonella infections (paratyphoid).
7. Acute brucellosis with bacteremia.
8. Tularemia.
9. Bacterial endocarditis due to Gram-negative bacilli.

The following diseases are not being investigated at the present:

1. Chronic idiopathic ulcerative colitis.
2. Lupus erythematosis acutus disseminatus.
3. Leukemia.
4. Cancer
5. Fever of unknown cause.
6. Rheumatic fever.
7. Rheumatoid arthritis.

Some cases of tuberculosis are being treated but until the supplies are more plentiful the program is rather limited.

The development of penicillin and penicillin products has advanced rapidly since its release for unlimited civilian use a year ago. Since that time many dosage forms have been placed on the market. These include tablets, pastilles, ointments and various parenteral forms. Several vehicles such as Emulgen of Lakeside Laboratories and Solvecillin of Solvecillin, Incorporated, have been placed on the market. So much literature has appeared on these preparations that they will not be discussed here.

Recent reports have shown that of the four types of penicillin contained in the commercial products now available, one (penicillin K) has a lower therapeutic activity. These penicillins (F, G, K and

X) differ slightly in the nature of a side group attached to their common chemical nuclear structure.

Most commercial penicillins at first consisted largely of penicillin G. Later studies of products produced by different strains of *Penicillium* and under varying processes revealed the presence of the other types F, K, and X. Their reported bactericidal activity *in vitro* varied, against *Staphylococcus aureus, Spirochoeta pallida,* and hemolytic streptococci. *In vivo* results in experimental syphilis did not bear out the expected relationship. For a period, because of the pressing demand for more and a purer penicillin, producers began obtaining a penicillin higher in K content.

Penicillin K is apparently excreted and destroyed more rapidly than the others and is therefore relatively ineffective (about 1:10 in comparison with F, G, and X) against syphilis and other infections. Chesney found pure penicillin K of no value in syphilis in rabbits.

The need for minimizing the content of K in commercial penicillins is now recognized. Standardization of impure penicillin mixtures by some method other than *in vitro* bactericidal activity seems necessary. However, commercial penicillin is the best and safest treatment of syphilis yet devised. Patients who have been treated with it during the past several years and their doctors need not be alarmed over recent sensational reports of its being ineffective. This is particularly true of the usual range of infections and primary stages of syphilis. Commercial penicillin has not consisted of pure K. However, it is possible that the presence of K in penicillin may account for resistance to penicillin which some organisms have developed and the difficulty in curing subacute bacterial endocarditis with penicillin.

Resistance

Aware of the growing importance of acquired resistance to chemotherapy on the part of infectious micro-organisms, the medical research workers and practitioners have studied the problem. Development of "fast" or drug-resistant organisms was noted to an appreciable extent for the first time in connection with the sulfonamides.

An organism may be normally susceptible to chemotherapy such as by the sulfonamides. Occasionally, strains of micro-organisms have been noted which seem to have or to develop an immunity to this chemotherapy. The immunity is selective. It is believed to be brought about by continued exposure of the strains to amounts of the drug

insufficient to inhibit or destroy their growth. When this occurs, sulfonamide-resistant and a drug-resistant strain or drug-fast organism is produced.

Most chemotherapeutic agents have produced at some time, resistant strains. This resistance is usually transitory but in some cases the fastness is permanent. The danger from sulfonamide resistance was somewhat eliminated by penicillin therapy. However, penicillin-resistant strains are now being reported. Strains of organisms resistant to sulfonamides are usually amenable to penicillin therapy and in turn penicillin-resistant organisms are usually amenable to treatment by sulfonamides. No extensive studies have been reported concerning resistance to streptomycin but it is believed that this drug will not differ in this respect from penicillin. The rate of development of resistance to streptomycin as noted in a few studies was much faster.

Infections with streptomycin-resistant strains continued *in vivo* and could not be controlled by the largest doses of the drug tolerated by animals. However, again a selective resistance was noted and it was observed that *in vivo* and *in vitro* strains resistant to either penicillin or streptomycin were found susceptible to the other.

These observations suggest that streptomycin and penicillin act on these micro-organisms in quite different ways. This conclusion is supported by three other differences in the behavior of gonococci and meningococci toward streptomycin and penicillin: (a) the more rapid acquisition of streptomycin resistance, (b) the absence in streptomycin resistant gonococci and meningococci of the gross physical change and abnormal microscopic appearance of penicillin resistant micro-organisms and (c) the retention or even enhancement of virulence of meningococci after acquiring streptomycin resistance, whereas the development of penicillin resistance tends to lower their virulence somewhat.

Although in clinical fields naturally streptomycin-resistant strains as yet have not been reported, it is possible that such will ultimately develop.

Physicians and pharmacists interested in streptomycin as an effective agent for the treatment of specific indicated conditions will carefully provide against the administration of insufficient doses. The administration of penicillin, the sulfonamides and now streptomycin seems to require adequate dosage. When quantities are insufficient

to accomplish therapeutic objectives, the results are as dangerous as the infection.

It is apparently axiomatic in therapy with the antibiotic agents that dosage must be adequate to accomplish the desired end result of inhibition or destruction of the infectious organisms. If the quantities of the drugs employed are not "in excess" of the required therapeutic quantity, either through ignorance on the part of the prescriber or false economy in limiting the amount of the drug used, serious damage to the welfare of the patient will result, and the development of resistant strains is almost inevitable.

GLYCERINE JELLY BASE FOR PENICILLIN

Special advantages and superior action are obtained when penicillin is applied on a nongreasy glycerine jelly, according to a report by J. Spencer, E. J. Bishop and A. Ricks (*Lancet* 1:127, 1946). The jelly is made by gradually mixing 110 cc. of glycerine with 8 Gm. of powdered tragacanth in a dry mortar and pouring the mixture slowly into a jar containing 332 cc. of an 0.25 per cent solution of methyl-para-hydroxy-benzoate (Nipagin M). It is placed then in an autoclave and allowed to steam for ten minutes, after which it is sterilized at 10-pounds pressure for 30 minutes. When cool, 250,000 units of penicillin, dissolved in enough sterile distilled water (about 25 cc.), is added to make a total weight of 500 Gm. of jelly.

Spencer, Bishop and Ricks claim the following advantages for the jelly: (1) It infiltrates damaged and diseased tissue readily and easily; (2) the ingredients are readily and cheaply available; (3) the presence of glycerine, which is hygroscopic, has a dehydrating effect in inflammatory conditions and increases the penetrative action of the drugs held in solution; and, (4) it is easy to manipulate by spreading or pouring on skin lesions, wounds, sinuses or open cavities. Anent this last point, it is noted that the consistency of the jelly may be varied by regulating the amount of tragacanth.

SELECTED ABSTRACTS

German Pharmaceutical Formulae: Details of I. G. Specialties. (Editor.) *Pharm. J. 102,* 172 (1946). The data presented have been excerpted from reports submitted by technical teams which investigated I. G. factories. It is emphasized that the processes may be protected by British patents or patent applications.

Barrier Cream. The following product, termed "Creme N," was considered effective as a barrier cream for use in industrial hygiene; it contained stearine 10 per cent, emulgator (stearine glycol ester) 3 per cent, glycerogen 12 per cent, starch 8 per cent, *p*-hydroxybenzoic acid ester 0.3 per cent, essential oil 0.4 per cent, distilled water to 100 per cent.

Glycerogen is stated to consist of glycerin 40 per cent, propylene glycol 40 per cent and hexahydric alcohols 20 per cent. It is believed that glycerogen is prepared by the hydrogenation of invert sugars at 200° under a pressure of 300 atmospheres with nickel or pumice as catalyst.

Atebrin Tablets. The formula used for the granulation contained atebrin (100 per cent) 57 Kg., maize starch 22 Kg., amylose 1 Kg. and talc 29 Kg. The ingredients were mixed, granulated with cold water, forced through a 1.2 mm. sieve, and dried. A separate granulation was then prepared by adding 3 Kg. of atebrin to a mixture of 11 Kg. of talc and 0.72 Kg. of melted cocoa butter and forcing through a 0.4 mm. sieve. The two granulations were then mixed and passed through a 1.2 mm. sieve; after determination of the water content, the mixture was made up to 132 Kg. The finished tablets, each weighing 0.22 gm., contained 0.100 gm. of atebrin.

Plasmochin Tablets. These tablets weighed 0.16 gm. each and contained 0.02 gm. of the drug. Maize starch and talc were included in the granulation.

Asthma Inhalant. A preparation called "Aspasan" contained N-(γ:γ-diphenylpropyl) piperidine hydrochloride 50 gm., racemic dihydroxyephedrine hydrochloride 5 gm., 4-hydroxyephedrine hydrochloride 10 gm., acetone bisulfite 2 gm., vanillin 0.5 gm., glycerin 200 gm. and water to 1000 gm.

The spasmolytic action of diphenylpropylpiperidine is said to be slower than that of ephedrine, but more prolonged. Acetone bisulfite is used as a stabilizer.

Mosquito Repellents. Among the repellents tested against *Aedes aegypti* and *Culex fatigans* was "Presinol" or "Mipex," which contained cinnamyl alcohol 100 gm., ethyl alcohol 894 gm., calcium chloride (90-93 per cent) 60 gm., magnesium chloride 40 gm., melissa oil 1 gm., geraniol 0.5 gm. and water 106 gm.

The use of calcium chloride was found to extend the repellent time of cinnamyl alcohol, coumarin, phthalic acid esters, etc.

A preparation which was considered to be more effective than diethylphthalate contained the following: trichloracetylchlorethylamide 7.5 per cent, calcium chloride 1.25 per cent, magnesium chloride 1.25 per cent, absolute alcohol 60 per cent and water 30 per cent.

Depot Insulin. It is claimed by the Germans that an insulin preparation containing Surfen A (an amino quinoline urea) is clinically more satisfactory than protamine insulin preparations. This product contained insulin 40 units, glucose 40 mg., chloretone 5 mg. and Surfen A 0.166 mg.

Vigantol Dragees. Vigantol (vitamin D_2) was administered in doses of 0.1 mg. by means of dragees containing sugar, cocoa, tragacanth, vanillin, alcohol and Ceylon cinnamon.

Periston for Transfusion. The German claim that a product termed Periston is equal to blood plasma as a blood substitute is regarded by the British investigators as unfounded. The active constituent of Periston is Kollidon, a polymer of N-vinyl-pyrolidone-2. The solution, which was sterilized by heating at 120°, contained the following: sodium chloride 800 gm., potassium chloride 42 gm., calcium chloride (hexahydrate) 50 gm., magnesium chloride (hexahydrate) 0.5 gm., N/50 hydrochloric acid 1710 mils, sodium bicarbonate 168 gm., Kollidon solution (20 per cent) 12,500 mils and distilled water to 100 liters.

Periston remains in the circulation in significant quantities for two or three days after injection. It is excreted by the kidneys at a rate of about 50 per cent a day, although only about 50 per cent could be accounted for in this way. It has been suggested that only the smaller molecules (up to a molecular weight of 10,000) are excreted.

The British authorities believe that Periston is superior to normal saline solution or acacia, and advise that comparisons with ungraded gelatin should be made in order to evaluate the German claims of its superiority to the latter substance.

SOLID EXTRACTS

The synthesis of sucrose from levulose and dextrose utilizing an enzymatic reaction has been announced. Until now attempts to combine dextrose and levulose by strictly chemical means have been unsuccessful. The enzyme accomplishing this synthesis is liberated by the bacterium *Pseudomonas Saccharophilia.* Evidence has been accumulating to show that dietary sucrose behaves in quite a different way than an equivalent mixture of dextrose and levulose. Now that sucrose synthesis is possible from its components its study throughout metabolism may be accomplished by using radioactive carbon containing in one of its component parts.

AJP

The popularity of the so-called "cold wave" as a substitute for that produced using heat has resulted in a number of poisoning cases among women. The agent responsible is thioglycolic acid toward which some persons show sensitivity. A patch test to determine those sensitive or allergic to this ingredient is considered advisable and care should be exercised to prevent undue contact of the solution with the skin or scalp. The potential hazard places considerable responsibility on the manufacturer in labelling the product.

AJP

The theory has been advanced that sensitivity to penicillin by individuals never before having contact with it may be due to a pre-existing fungus infection. Thus a sufficient amount of penicillin-like compounds would be formed to sensitize the individual to penicillin when used at a later date.

AJP

A hormone-like selective weed killer is now commercially available. Chemically it is 2, 4 dichlorophenoxyacetic acid. It is applied in solution as a spray and it is absorbed into the plant where it kills by interfering with the metabolism of food conversion. It is effective against most broad-leafed weeds such as dandelions, morning glory, burdock, etc., without affecting grass.

BOOK REVIEWS

Cosmetics and Dermatitis. By Louis Schwartz, M. D., and Samuel M. Peck, M. D. 189 pages incl. index. Paul B. Hoeber, Inc., New York. Price: $4.00.

The authors, both of whom are connected with the United States Public Health Service, are also quite well experienced in the field of dermatology.

The first chapter is a rather concise and easily understandable discussion of the anatomy and physiology of the skin and its appendages, i. e., the hair and nails. The authors then take up the subject of allergic dermatoses followed by occupational dermatitis and finally dermatitis caused by cosmetics. The whole field of cosmetics is covered, not only the commonplace items such as powder, lipstick and creams but soaps, suntan preparations, perfumes, hair preparations, etc.

Written in a clear and not too technical style this little book should prove a useful one to many in the cosmetic industry. Too often the possible hazard of cosmetic ingredients is overlooked by those concerned only with making an attractive product.

Those who review advertising copy will also find in the book information that will help them in avoiding extravagant claims for their products.

L. F. TICE.

Introduction to Emulsions. By George M. Sutheim. 260 pages incl. index. Chemical Publishing Co., Brooklyn, N. Y. Price: $4.75.

This book on emulsions is based on a series of lectures given on the subject by the author at the Brooklyn Polytechnic Institute. It is written in a rather practical style and yet enough theory is contained to explain fundamental concepts and behavior of emulsion systems.

Those who are concerned with practical problems in emulsion manufacture will find the book written in such a way as to be easily understood and useful and obviously the work of one who has had considerable experience in this field. For this reason it is a good companion volume to the more theoretical books on the subject such as the well-known classic by Clayton.

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